REMARKS/ARGUMENTS

Claims 5-6 and 21-35 are currently pending in the application. Claims 5-6 and 21-35 stand rejected. In view of the remarks provided below, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Brief Background of the Application

The present invention is directed to methods of using certain compounds and pharmaceutical compositions for treating depression.

35 U.S.C. § 103(a) Obviousness Rejection

Claims 5-6 and 21-35 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Mueller et al. (PCT Publication No. WO 96/40097, hereinafter "Mueller") in view of Skolnick et al. (Pharmacopsychiatry, abstract, 1996 January, 29:1, 23-6, hereinafter "Skolnick"). Applicant respectfully traverses this rejection, as set forth below.

M.P.E.P. 706.02(j) sets forth the standard for a Section 103(a) rejection:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). (Emphasis added).

The 35 U.S.C. § 103(a) obviousness rejection of claims 5-6 and 21-35 is improper, and the examiner has not provided a *prima facie* case of obviousness, because the combination of Mueller and Skolnick does not provide a reasonable expectation that compounds recited in the claims will treat depression.

The Office Action states that Mueller discloses that certain compounds 20, 60, 65, and 142 (WO 96/40097, pages 62, 64, 62-64, 255-256; claims 1, 18-19, 77, and 80; Tables 5-7 and 9) are NMDA receptor antagonists The Office Action also states that Skolnick teaches that the NMDA receptor is "involved in the pathophysiology of depression," and that NMDA receptor

antagonists "mimic the effects of clinically effective antidepressants" (Office Action, p. 5, *citing* Skolnick abstract). The Office Action concludes that one having ordinary skill in the art would have expected that "the downregulation of NMDA receptor by NMDA antagonist would provide clinical utility in the treatment of depression" (Office Action, p. 5).

Applicants traverse the rejection on the grounds that the combination of Mueller and Skolnick does not provide one of ordinary skill in the art with a reasonable expectation that the claimed compounds would treat depression since: (1) Skolnick does not provide sufficient to data to provide a reasonable expectation that all NMDA receptor antagonists would treat depression and (2) empirical data indicates that many NMDA receptor antagonists do not possess antidepressant activity. Based on the limited data of Skolnick and the contrary empirical data submitted with this response, one of ordinary skill in the art would not have had a reasonable basis for expecting any particular NMDA receptor antagonist to exhibit antidepressant activity. Even the Skolnick reference itself admits there is uncertainty whether NMDA receptor antagonists necessarily have antidepressant activity.

A. Empirical data shows that some compounds active at the NMDA receptor do not have antidepressant activity.

Empirical data shows that some compounds active at the NMDA receptor do not have antidepressant activity. This empirical data includes data from third parties published in the art and data obtained through the Applicant's own research. As a result, one skilled in the art would not have a reasonable expectation that the compounds recited in the present claims which have NMDA receptor antagonist activity would treat depression.

Applicant submits with this response a Declaration by Dr. Alan Mueller, one of the inventors of the present application. The Declaration by Dr. Mueller includes Exhibits C and D provide third-party data showing that certain compounds that bind the NMDA receptor do not have antidepressant activity. The Declaration also includes Exhibit B which provides data showing that certain NMDA receptor antagonists do not have antidepressant activity. Each of these exhibits is discussed in further detail below.

1. Panconi et al. teaches that certain NMDA receptor antagonists do not have antidepressant activity.

Exhibit C of the Declaration is a scientific article by Panconi et al. (*Pharmacology Biochemistry and Behavior*, Vol. 46, pp. 15-20, 1993, hereafter "Panconi"). Panconi investigated four NMDA receptor antagonists for antidepressant activity. The antagonists were MK-801, 2-amino-7-phosphonoheptanoic acid (AP7), kynurenic acid, and 1-glutamic acid diethylester (GDEE) (Abstract). Panconi's teaches that three out of four NMDA receptor antagonist compounds (all but MK-801) did not show antidepressant activity using the tail suspension test (TST) (page 18, last paragraph). Panconi also teaches that while the fourth NDMA receptor antagonist MK-801 significantly reduced the duration of immobility in both the tail suspension and forced swim tests in mice, the mechanism for its activity may be explained by an increase in locomotor activity not directly related to the NMDA receptor (page 18, first paragraph).

Panconi concludes that one cannot predict whether NMDA receptor antagonists will treat depression. Specifically, Panconi states, "investigations ([in the] reserpine, apomorphine, and yohimbine tests) could not confirm the suspected antidepressant activity" of MK-801, and that results from other NMDA antagonists "throw doubt concerning the potential antidepressant activity of MK-801 and other NMDA antagonists" (Abstract). Panconi further states, "[a] definitive answer as to whether functional antagonists at the NMDA receptor complex represent potential antidepressants cannot be given" (page 19, last paragraph). Panconi, therefore, provides examples of NMDA receptor antagonists that do not have antidepressant activity and teaches away from the claimed invention. In view of Panconi, one skilled in the art would not reasonably expect a compound that binds the NMDA receptor would treat depression.

2. Additional data published by Zarate et al. also shows that other NMDA receptor antagonists lacks antidepressant activity.

Exhibit D of the Declaration is a scientific article by Zarate et al. (*Am. J. Psychiatry* 163:153-155, January 2006, hereafter Zarate). Zarate investigated another NMDA receptor antagonist memantine for antidepressant activity (Abstract). Zarate's research included a parallel-group, placebo-controlled trial of memantine, to determine efficacy in the treatment of major depressive disorders (Description). Zarate found that despite memantine's ability to bind

the NMDA receptor, it "was not effective in the treatment of major depressive disorder" (Abstract).

Zarate, therefore, provides another example of a NMDA receptor antagonist that does not have antidepressant activity. Again, one skilled in the art would not reasonably expect that if a compound binds the NMDA receptor, it would treat depression.

3. Additional data obtained by the Applicant also shows NMDA receptor antagonists that do not have antidepressant activity.

Exhibit B of the Declaration is a table showing additional examples of compounds that bind the NMDA receptor but do not have antidepressant activity. The table identifies six compounds, i.e., compounds 50, 65, 118, 119, 156, and 186 examined by Dr. Mueller and listed in the present application that bind to the NMDA receptor. The affinity measurements were performed in a [^{3}H]MK-801 NMDA receptor binding assay, substantially as described in Example 1 of the Specification of the present application (*see* Exhibit B, column 4). The data in both Exhibit B and the Specification shows that compounds 50, 65, 118, 119, 156, and 186 bound to the NMDA receptor (IC_{50} (μM) vs. NMDA [^{3}H]MK-801) with values of 0.762, 2.0, 0.240, 0.087, 0.090, and 0.123, respectively. The same compounds were assayed in a forced-swim test (FST), substantially as described in Example 2 of the Specification of the present application (*see* Exhibit B, last column 9). The data in Exhibit B further shows that compounds 50, 65, 118, 119, 156, and 186 resulted in reduced-duration-of-immobility assay values of 38%, 33%, 21%, 32%, 14%, and 33%, respectively. Dr. Mueller's declaration states that the above results show statistically significant absence of antidepressant activity.

In summary, the Exhibits B, C, and D each provide evidence that many NMDA receptor antagonists do not have antidepressant activity. This information contradicts the assertion in the Office Action that NMDA receptor antagonists would reasonably be expected to have antidepressant activity. One of ordinary skill in the art would not, therefore, have a reasonable expectation that compounds recited in the claims would also have antidepressant activity. The claimed methods of treating depression, therefore, are not obvious in view of Skolnick and Mueller.

B. The fact that *some* compounds having NMDA receptor antagonist activity does not imply that *all* compounds having NMDA receptor activity treat depression.

The Office Action asserts that that one skilled in the art could expect that all NMDA receptor antagonists will have an antidepressant activity. Not only is this assertion controverted by the above data, but it also is not supported by Skolnick itself. Skolnick discloses that 17 antidepressant compounds bind to the NMDA receptor. Skolnick, at best, suggests that compounds which are known antidepressants will bind the NMDA receptor. Skolnick does not suggest that compounds that bind the NMDA receptor will also treat depression.

First, Skolnick acknowledges that there is uncertainty in predicting whether an NMDA receptor antagonist will possess an antidepressant property. Skolnick actually teaches that the relationship between NMDA receptor antagonist activity and antidepressant activity is not established:

> "chronic [antidepressant] treatments *may produce multiple, discrete effects at NMDA receptors, or may exert differential effects at NMDA receptor subtypes*. The relative contribution or importance of these effects to either the onset of antidepressant action or efficacy *are unknown*, but raise important questions for future study."

(Page 25, first full paragraph, *emphasis added*). Thus, even if a compound is a known, NMDA receptor antagonist, the affect, if any, of any such compound on depression is unclear, perhaps because the receptor has multiple binding sites, multiple subtypes, and is expressed in different biological roles. Thus, although Skolnick suggests that the NMDA receptor "is involved" in the physiology of depression, Skolnick admits that it is uncertain whether NMDA receptor antagonists will treat depression. Skolnick, therefore, fails to support the conclusion that one of ordinary skill in the art would have a reasonable expectation that the claimed methods of treating depression will be successful.

Second, the reasoning offered in the Office Action is based on a fallacy in logic. The mere fact that *some* compounds having antidepressant activity are active at the NMDA receptor does not mean that *all* compounds active at the NMDA receptor would reasonably be expected to have antidepressant activity. With respect to the references relied upon in support of the rejection, Skolnick states that 17 different compounds known to have antidepressant activity also produced changes in one or both of two neurochemical measures ([^{3}H]5,7-DCLA binding and the effect of glycine [^{3}H]CGP 39653 binding in cortical tissues). Based on these results,

Skolnick postulated: "we *propose* that adaptive changes in NMDA receptors *may* be the final common pathway for antidepressant action." (Abstract; emphasis added). The mere fact that 17 different compounds known to have antidepressant activity were active that the NMDA receptor, however, does not imply that *all* compounds known to have antidepressant activity are active that the NMDA receptor or that *all* compounds active at the NMDA receptor will also have antidepressant activity.

Furthermore, Skolnick does not teach or suggest that the 17 compounds are representative the entire class of antidepressant compounds. Nor does the office action provide any scientific data or rational to support the assumption that all NMDA receptor antagonists would be expected to have antidepressant activity. As established above, some compounds active at the NMDA receptor actually do not have antidepressant activity.

Since the reference relied upon teaches that it is still unpredictable what effects and NMDA receptor antagonist will have on depression, and the reasoning in the Office Action is logically flawed, and is, in any event, contradicted by empirical data, one of ordinary skill in the art would not have had a reasonable expectation that the claimed compounds would also have antidepressant activity. The claimed methods of treating depression, therefore, are not obvious, and the Applicant respectfully requests that the rejection be withdrawn and the claims allowed. Applicant respectfully requests that the rejection be withdrawn and the claims allowed.

CONCLUSION

In view of the above remarks, Applicant submits that the claimed invention is patentably distinct over the cited art. Applicant, therefore, requests that the rejection be withdrawn and the claims allowed. Should the examiner determine that additional issues remain which might be resolved by a telephone conference, he is respectfully invited to contact Applicant's undersigned attorney.

Respectfully submitted,

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